**PATENT**
**CUSTOMER NO: 32425**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:
Ben SHEN
Hyung-Jin KWON

Serial No.: 10/646,664

Filed: August 22, 2003

For: METHODS OF DIRECTING C-O BOND FORMATION UTILIZING A TYPE II POLYKETIDE SYNTHASE SYSTEM

Group Art Unit: 1656

Examiner: C-M. Kam

Atty. Dkt. No.: WARF:032US

Confirmation No.: 3619

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October 22, 2007
Date

Steven L. Highlander

# SUPPLEMENTAL APPEAL BRIEF

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**APPEAL BRIEF**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-01450

Dear Sir:

This Brief is submitted in response to the Notification of Non-Compliant Appeal Brief (37 CFR 41.37) mailed on September 21, 2007. The deadline for this supplemental brief is October 21, 2007. It is believed that no fees are due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.121 be required for any reason relating to this document, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/VBLT:007USC1/SLH.

## I. Real Party In Interest

The real party in interest is the assignee, the Wisconsin Alumni Research Foundation, Madison, WI.

## II. Related Appeals and Interferences

There are no related appeals or interferences.

## III. Status of the Claims

Claims 1-25 were filed with the original application, and claims 19 and 20 have been cancelled. Claims 1-18 and 21-25 are thus pending, rejected and are appealed. A copy of the appealed claims is attached as Appendix A.

## IV. Status of the Amendments

The "after final" amendments were entered by the examiner.

## V. Summary of the Claimed Subject Matter

Claim 1 is drawn to a method of modifying a biological molecule by formation of a C--O bond comprising the step of contacting a biological molecule with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 2; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under highly stringent conditions to SEQ ID NO: 2 and catalyzes C--O bond formation; wherein said biological molecule is a substrate for said polypeptide, and whereby said

polypeptide modifies the biological molecule by formation of a C--O bond. Support can be found in the Specification at page 3, lines 2-14.

Claim 10 is drawn to a method of catalyzing a C--O bond between biological molecules comprising the step of contacting biological molecules with at least one polypeptide encoded by a nucleic acid comprising the sequence set forth in SEQ ID NO: 1, or by a nucleic acid hybridizing under stringent conditions thereto, said biological molecules being substrates for said at least one polypeptide, whereby said polypeptide catalyzes C--O bond formation between the biological molecules. Support can be found in the Specification at pages 4-5, bridging paragraph.

Claim 17 is drawn to a method of producing a macrotetralide or a macrotetralide analogue comprising the steps of (i) contacting enantiomeric nonactins or analogs thereof with at least one polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3 or 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 2 or 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under very stringent conditions to SEQ ID NO: 2 or 4 and catalyzes C--O bond formation; under conditions such that the polypeptide catalyzes C--O bond formation between the enantiomeric nonactins or analogs thereof, whereby a macrotetralide or macrotetralide analogue is thereby synthesized; and (ii) recovering said macrotetralide or macrotetralide analogue. Support can be found in the Specification at page 5, lines 4-14.

Claim 21 is drawn to a method of catalyzing C--O bond formation between biological molecules comprising the step of contacting biological molecules with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in

SEQ ID NO: 3; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 2; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under very stringent conditions to SEQ ID NO: 2 and catalyzes C--O bond formation; wherein said biological molecules are substrates for said polypeptide, whereby said polypeptide catalyzes C--O bond formation between the biological molecules. Support can be found in the Specification at page 6, lines 10-19.

Claim 23 is drawn to a method of catalyzing C--O bond formation between biological molecules comprising the step of contacting biological molecules with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO: 4 and catalyzes C--O bond formation; wherein said biological molecules are substrates for said polypeptide, whereby said polypeptide catalyzes C--O bond formation between the biological molecules. Support can be found in the Specification at paragraph bridging pages 6-7.

Claim 25 is drawn to a method of chemically modifying a biological molecule by formation of a C--O bond comprising contacting a biological molecule with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3 or 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 2 or 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO: 2 or 4; wherein said biological molecule is a substrate for said polypeptide, whereby said polypeptide chemically

modifies the biological molecule by formation of a C--O bond. Support can be found in the Specification at page 7, lines 7-18.

## VI. Grounds of Rejection to be Reviewed on Appeal

1. Claims 1-18 and 21-25 stand rejected as allegedly lacking an enabling disclosure sufficient to satisfy 35 U.S.C. §112, first paragraph.
2. Claims 1-18 and 21-25 stand rejected as allegedly lacking written description sufficient to satisfy 35 U.S.C. §112, first paragraph.

## VII. Argument

### *A. Standard of Review*

Findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. §706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *In re Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312. Accordingly, it necessarily follows that an examiner's position on appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

### *B. Rejection for Alleged Lack of Enablement*

Claims 1-18 and 21-25 are rejected as lacking enablement for sequences that hybridize to SEQ ID NO:1, 2 or 4 "under various stringent conditions" and catalyze C-O bond formation. Interestingly, in attempting to provide the basis for the rejection while addressing each of the factors set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), the examiner can seem to find

only one substantive problem with the specification, that being the absence of specific examples of sequences that hybridize to SEQ ID NO:1, 2 or 4. The examiner repeats this alleged "deficiency" no less than six times in addressing the seven *Wands* factors. Appellants submit that this myopic view of enablement is not justified by the relevant case law.

The proper question to be asked here is whether one of skill in the art would find it necessary to conduct ***undue*** experimentation to arrive at the present invention. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Appellants submit that one the functional SEQ ID NOS:1, 2 and 4 have been found, it is a trivial matter to identify sequences that hybridize under ***stringent*** conditions, which conditions select for a relatively small number of possible sequences that exhibit ***high homology*** to SEQ ID NOS:1, 2 and 4. Once such sequences have been identified, it requires no more than introducing such sequences into an expression system to determine whether they have the requisite enzymatic activity.

Now, returning to the *Wands* factors, appellants submit that the claims are not nearly as broad as the examiner suggests – limited to sequence that hybridize to know enzymatic sequences only under stringent conditions. And while working examples are not provided, it also is black letter law that examples are not necessary to establish enablement. The state of the art is quite high, and in contrast to the examiner's assertion, the ability to easily screen and test sequences for hybridization and enzymatic activity means that this factor too weighs in favor of

enablement. While the biological arts are considered unpredictable, appellants' claims here have been limited to only those sequences that hybridize ***and*** catalyze C-O bond formation. The amount of guidance provided also is quite high, given that one need only follow routine experimental procedures to identify hybridizing sequences that also retain enzyme function. Finally, the nature of the invention is straightforward – nucleic acid sequences – and cannot be considered an impediment to enablement.

In sum, the examiner's ***only*** argument against enablement is that appellants have not ***shown*** that the claimed hybridizing sequences with enzymatic sequences exist. However, this fact alone cannot dominate the enablement analysis in the way argued by the examiner. In contrast, it should be by now well-established that finding sequence homologs in bacteria using hybridization techniques is more than routine. As such, appellants submit that the claims are, indeed, enabled. Reversal of the rejection is therefore respectfully requested.

### *C. Rejection for Alleged Lack of Written Description*

Claims 1-18 and 21-25 are rejected as lacking written description. The examiner's ***only*** argument is that "the specification has not disclosed a genus of variants for functional polypeptides encoded by" SEQ ID NO:1, 2 or 4. Yet this statement is on its face incorrect, in that appellants indeed ***do*** disclose a genus, defined precisely by sequences that hybridize under stringent conditions to SEQ ID NO:1, 2 or 4. While the examiner likely means that appellants do not disclose a number of species within that genus, that factor alone is not dispositive.

It is well established that sufficiency of written description is established by whether those of skill in the art would view appellants as being in possession of the invention – generic or specific – at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570,

1575, 227 USPQ 177, 179 (Fed. Cir. 1985) ("The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'"; quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). The examiner has adduced no evidence on this point, and appellants submit that as of 2002, the ability of the skilled artisan to perform hybridization analysis on bacterial DNA cannot be challenged. Moreover, the fact that related bacterial species contain structurally related genes is also beyond question.

In sum, this rejection is much like the one against enablement – narrowly premised on a single perceived defect that ignores the broader legal tenets of support. Long before *Eli Lilly* was decided, the Federal Circuit and its predecessor court clearly set forth that reciting litany of species falling within a genus is not the only way to describe that genus. Here, using a well-known technique as a proxy for structural homology, appellants have done just that. Reversal of the rejection is therefore requested.

### *D. Conclusion*

In light of the foregoing, appellants respectfully submit that all pending claims are enabled and adequately described by the specification as filed. Therefore, it is respectfully requested that the Board reverse each of the pending rejections.

Respectfully submitted,

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Date: October 22, 2007

## VIII. APPENDIX A – APPEALED CLAIMS

1. A method of modifying a biological molecule by formation of a C--O bond comprising the step of contacting a biological molecule with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 2; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under highly stringent conditions to SEQ ID NO: 2 and catalyzes C--O bond formation; wherein said biological molecule is a substrate for said polypeptide, and whereby said polypeptide modifies the biological molecule by formation of a C--O bond.

2. The method according to claim 1, further comprising the step of contacting the biological molecule modified by the polypeptide recited in claim 1 with a second polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO: 4 and catalyzes C--O bond formation; whereby said second polypeptide further modifies the biological molecule by formation of a C--O bond.

3. The method according to claim 1, wherein the C--O bond formed is between the biological molecule and a second biological molecule, said second biological molecule also a substrate for the polypeptide.

4. The method according to claim 1, wherein said contacting occurs in a host cell.

5. The method according to claim 4, wherein said host cell is a bacterium.

6. The method according to claim 4, wherein the host cell is a eukaryotic cell selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

7. The method according to claim 4, wherein said biological molecule is ~~an~~ exogenously supplied.

8. The method according to claim 1, wherein the contacting is *ex vivo*.

9. The method according to claim 1, wherein said biological molecule is an enantiomeric nonactin or analog thereof.

10. A method of catalyzing a C--O bond between biological molecules comprising the step of contacting biological molecules with at least one polypeptide encoded by a nucleic acid comprising the sequence set forth in SEQ ID NO: 1, or by a nucleic acid hybridizing under stringent conditions thereto, said biological molecules being substrates for said at least one polypeptide, whereby said polypeptide catalyzes C--O bond formation between the biological molecules.

11. The method according to claim 10, wherein said contacting is in a host cell.

12. The method according to claim 11, wherein said host cell is a bacterium.

13. The method according to claim 11, wherein said host cell is a eukaryotic cell selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

14. The method according to claim 11, wherein at least one of said biological molecules is an exogenously supplied substrate.

15. The method according to claim 10, wherein the contacting is *ex vivo*.

16. The method according to claim 10, wherein said biological molecule is an enantiomeric nonactin or analog thereof.

17. A method of producing a macrotetralide or a macrotetralide analogue comprising the steps of (i) contacting enantiomeric nonactins or analogs thereof with at least one polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3 or 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 2 or 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under very stringent conditions to SEQ ID NO: 2 or 4 and catalyzes C--O bond formation; under conditions such that the polypeptide catalyzes C--O bond formation between the enantiomeric nonactins or analogs thereof, whereby a macrotetralide or macrotetralide analogue is thereby synthesized; and (ii) recovering said macrotetralide or macrotetralide analogue.

18. The method according to claim 17, wherein said method is carried out in a host cell and the enantiomeric nonactins or analogs thereof are exogenously supplied.

21. A method of catalyzing C--O bond formation between biological molecules comprising the step of contacting biological molecules with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 2; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under very stringent conditions to SEQ ID NO: 2 and catalyzes C--O bond formation; wherein said biological molecules are substrates for said polypeptide, whereby said polypeptide catalyzes C--O bond formation between the biological molecules.

22. The method according to claim 21, wherein said method is performed in a host cell and at least one of the biological molecules is an exogenously supplied substrate.

23. A method of catalyzing C--O bond formation between biological molecules comprising the step of contacting biological molecules with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO: 4 and catalyzes C--O bond formation; wherein said biological molecules are substrates for said polypeptide, whereby said polypeptide catalyzes C--O bond formation between the biological molecules.

24. The method according to claim 23, wherein said method is performed in a host cell and at least one of the biological molecules is an exogenously supplied substrate.

25. A method of chemically modifying a biological molecule by formation of a C--O bond comprising contacting a biological molecule with a polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3 or 5; (b) a polypeptide encoded by a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 2 or 4; and (c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO: 2 or 4; wherein said biological molecule is a substrate for said polypeptide, whereby said polypeptide chemically modifies the biological molecule by formation of a C--O bond.

## IX. APPENDIX B – EVIDENCE CITED

None

## X. APPENDIX C – RELATED PROCEEDINGS

None